Claims

1. A compound having the formula

$$\mathbb{R}^{1}$$
 \mathbb{N}^{6}
 \mathbb{N}^{1}
 \mathbb{N}^{2}
 \mathbb{R}^{2}
 \mathbb{R}^{3}
 \mathbb{R}^{3}
 \mathbb{N}^{4}
 \mathbb{N}^{2}
 \mathbb{N}^{3}
 \mathbb{N}^{2}
 \mathbb{N}^{3}
 \mathbb{N}^{2}
 \mathbb{N}^{3}
 \mathbb{N}^{3}
 \mathbb{N}^{2}
 \mathbb{N}^{3}
 \mathbb{N}^{3}

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the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein:

m represents an integer being 0 or 1;

n represents an integer being 0, 1 or 2;

 R^1 represents hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl or C_{1-4} alkyl substituted with phenyl, pyridinyl or morpholinyl,

phenyl or phenyl substituted with one or where possible more substituents each independently being selected from C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, -NO₂ or cyano-

C₁₋₄alkyl,

piperidinyl or piperidinyl substituted with one or where possible more substituents each independently being selected from C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl or phenyl- C_{1-4} alkyl,

phenyl-C₁₋₄alkyl or C₁₋₄alkyloxycarbonyl;

20 R² represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl or hydroxy;

 R^3 represents hydrogen, phenyl, C_{1-4} alkyl or C_{1-4} alkyl substituted with phenyl or hydroxy; or

R² and R³ taken together with the carbon atom to which they are attached form a C₃₋₈cycloalkyl or Het¹ wherein said C₃₋₈cycloalkyl or Het¹ each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, phenylcarbonyl C₁₋₄alkylsulfonyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or -C(=NH)-NH₂;

R⁴ represents halo, hydroxy, hydroxyC₁₋₄alkyl or C₁₋₄alkyloxy;

R⁵ represents formyl, C₁₋₄alkyl, C₁₋₄alkyloxy, Het², -NO₂, -SO₂-Het⁶, aminosulfonyl, -SO₂-NR¹²R¹³,

C₁₋₄alkyl substituted with one or where possible more substituent being selected from hydroxy, halo, Het³, NR⁶R⁷ or formyl,

C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴, NR⁸R⁹ or -C(=O)-Het⁴;

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, -Het⁵, aminosulphonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkyloxyC₁₋₄alkyl, methoxyC₁₋₄alkyl or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, Het⁵, C₁₋₄alkyloxycarbonyl or C₁₋₄alkylsulfonyl;

 R^8 and R^9 are each independently selected from hydrogen, mono- or di($C_{1.4}$ alkyl)aminosulphonyl or aminosulphonyl;

 R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkyl,;

Het¹ represents piperidinyl;

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Het 2 represents a heterocycle selected from piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C_{1-4} alkyloxycarbonyl;

Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, hydroxyC₁₋₄alkyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, NR¹⁰R¹¹, imidazolyl, tetrahydropyrimidinyl, amino, NH₂-SO₂-O-, mono- or di(C₁₋₄alkyl)amino- SO₂-O-, NH₂-SO₂-NH-,

mono- or di(C_{1-4} alkyl)amino- SO_2 -NH- , hydroxy C_{1-4} alkyloxy C_{1-4} alkyloxy C_{1-4} alkyloxy;

R¹⁰ and R¹¹ are each independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, or mono- or di(C_{1-4} alkyl)aminosulfonyl;

Het⁴ represents a heterocycle selected from morpholinyl, piperidinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, aminosulphonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or C₁₋₄alkyl substituted with one or more hydroxy;

Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl, or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl;

Het⁶ represents morpholinyl.

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2. A compound according to claim 1 wherein;

10 R^1 represents C_{1-4} alkyl preferably methyl, C_{1-4} alkyl substituted with pyridinyl, phenyl, piperidinyl or piperidinyl substituted with C_{1-4} alkyloxycarbonyl;

R² represents hydrogen or C₁₋₄alkyl preferably methyl;

R³ represents hydrogen or C₁₋₄alkyl preferably methyl; or

 R^2 and R^3 taken together with the carbon atom to which they are attached form

cyclopentyl or piperidinyl wherein said cyclopentyl or piperidinyl each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, phenylcarbonyl or -C(=NH)-NH₂;

R⁴ represents halo or C₁₋₄alkyloxy;

20 R⁵ represents Het², C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, halo, Het³ or NR⁶R⁷, or R⁵ represents

 C_{1-4} alkyloxy substituted with one or where possible more substituents being selected from Het⁴ or -C(=O)-Het⁴;

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, Het⁵ or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

Het² represents piperazinyl;

Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C_{1-4} alkyl preferably methyl, aminosulfonyl, mono- or di(C_{1-4} alkyl)aminosulfonyl, hydroxy C_{1-4} alkyloxy C_{1-4} alkyl or C_{1-4} alkyloxy;

Het⁴ represents a heterocycle selected from morpholinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be

substituted with one, or where possible two or three C₁₋₄alkyl substituents, preferably methyl;

Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl.

3. A compound according to claim 1 wherein;

R¹ represents C₁₋₄alkyl preferably methyl, C₁₋₄alkyl substituted with phenyl, or R¹ represents piperidinyl or piperidinyl substituted with C₁₋₄alkyloxycarbonyl;

R² represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl;

R² represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl; or

R² and R³ taken together with the carbon atom to which they are attached form cyclopentyl or piperidinyl wherein said cyclopentyl or piperidinyl each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, C₁₋₄alkylsulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or phenylcarbonyl; R⁴ represents halo, preferably Cl or R⁴ represents C₁₋₄alkyloxy preferably methoxy;

R⁵ represents formyl, C₁₋₄alkyl substituted with one or where possible more substituent being selected from hydroxy, Het³ or NR⁶R⁷, or R⁵ represents C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴ or -C(=O)-Het⁴;

 R^6 and R^7 are each independently selected from hydrogen, $C_{1\text{-}4}$ alkyl, -Het⁵, $C_{1\text{-}4}$ alkylsulfonyl, methoxy $C_{1\text{-}4}$ alkyl, or $C_{1\text{-}4}$ alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

 Het^2 represents piperidinyl optionally substituted with $C_{1\text{--}4}$ alkyloxycarbonyl;

Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, hydroxyC₁₋₄alkyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, NR¹⁰R¹¹, imidazolyl, tetrahydropyrimidinyl, amino,

hydroxy C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl or C_{1-4} alkyloxy; R^{10} and R^{11} are each independently selected from hydrogen or C_{1-4} alkyl;

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Het⁴ represents a heterocycle selected from morpholinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three C₁₋₄alkyl substituents, preferably methyl;

Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl.

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- 4. A compound as claimed in any one of claims 1 to 3 wherein R^2 and R^3 taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl, preferably cyclopentyl.
- 5. A compound as claimed in any one of claims 1 to 4 provided that when R⁵ represents a C₁₋₄alkyloxy substituted with Het⁴, said Het⁴ is being selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with one C₁₋₄alkyl, preferably methyl.
- 6. A compound as claimed in any one of claims 1 to 4 provided that when R⁵ represents a C₁₋₄alkyloxy substituted with –C(=O)-Het⁴, said Het⁴ consists of piperazinyl preferably substituted with C₁₋₄alkyl.
- 7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective kinase inhibitory amount of a compound as described in any one of the claims 1 to 6.
 - 8. A process of preparing a pharmaceutical composition as defined in claim 7, characterized in that, a pharmaceutically acceptable carrier is intimately mixed with an effective kinase inhibitory amount of a compound as described in any one of claims 1 to 6.
 - 9. A compound as claimed in any one of claims 1 to 6 for use as a medicine.
- 10. Use of a compound as claimed in any one of claims 1 to 6 in the manufacture of a medicament for treating cell proliferative disorders such as atherosclerosis, restinosis and cancer.

- 11. A process of preparing a compound as described in claim 1, characterized by
 - i) reacting a primary amine of formula (V) with an aldehyde of formula (VI) in a condensation reaction using ethanol as a suitable solvent;

e) EtOH

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ii) followed by a nitrosative cyclisation of the thus obtained Schiffs bases of formula (II) with NaNO₂ in acetic acid, and refluxing the nitroso intermediates of formula (III) in a suitable solvent such as acetic anhydride or ethanol further comprising dithiothreitol (DTT);

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$$R_{1}$$

$$R_{2}$$

$$R_{3}$$

$$R_{1}$$

$$R_{3}$$

$$R_{4}$$

$$R_{2}$$

$$R_{1}$$

$$R_{3}$$

$$R_{2}$$

$$R_{3}$$

$$R_{4}$$

$$R_{2}$$

$$R_{3}$$

$$R_{4}$$

$$R_{2}$$

$$R_{3}$$

$$R_{4}$$

$$R_{5}$$

$$R_{6}$$

$$R_{1}$$

$$R_{1}$$

$$R_{3}$$

$$R_{2}$$

$$R_{3}$$

a) NaNO₂, AcOH, H₂O b) DTT, EtOH